Use of Data-Derived Uncertainty Factors in Human Risk Assessment

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Default uncertainty factors (UFs) of 10-fold have traditionally been used for extrapolation from animals to humans, and for accounting for variability of humans and protecting sensitive subpopulations. The process of human health risk assessment can be improved by improving the choice of UFs and moving away from these defaults, when supported by the scientific evidence. A first step away from defaults is the use of database-derived UFs, such as a categorical default based on characteristics of the substance or on species differences. Examples of such factors include the use of a UF of 3 for animal to human extrapolation for RfCs when dosimetric adjustments are done (U.S. EPA, 1994; Jarabek, 1994), or the use of the surface area adjustment for oral dosing. These approaches allow the replacement of defaults with chemical- and species-specific information, to improve the accuracy of the assessment. Renwick (1991) and Renwick and Lazarus (1998) suggested a default data-derived approach, in which the interspecies and intraspecies UFs were broken into toxicokinetic and toxicodynamic components, based on the relative contributions of these components in a number of chemicals. In the next step of incorporation of chemical-specific data, a fully data-derived approach uses chemical-specific toxicokinetic or toxicodynamic data to determine UFs (or adjustment factors) for that chemical.

Data-derived UFs allow the incorporation of chemical-specific data without requiring the detailed level of toxicokinetic information required to build a PBPK model. In addition, data-derived UFs can address toxicodynamic variability (intraspecies) or interspecies differences, which is more difficult to address with a toxicodynamic model. Several investigators have begun to address the criteria for the adequacy of data for replacement of default UFs (e.g., Meek, 2000), and a few assessments have been conducted using data-derived UFs (e.g., Dourson et al., 1998; IPCS, 1998). However, research into a number of issues is necessary before such factors can be broadly used. For example, criteria have not been developed on how to evaluate whether the critical determining factor has been identified. A number of researchers have looked at the ratios between animal and human toxicokinetic parameters, but it is unclear whether the factors so developed adequately describe the ratio between the animal and human tissue dose of the toxic agent. Similarly, it is currently unclear how to translate information on human variability in key metabolic parameters into an uncertainty factor for human variability in kinetics. Evaluation of PBPK models for model chemicals acting via selected modes of action may help to elucidate whether the distribution of certain parameters (e.g, the ratio of the mean and 95th percentile for a key enzyme's Vmax) adequately describe human variability. Identification of such generalizations will allow the broader use of data-derived UFs. Proposals are sought for projects that move forward the science of data-derived UFs. Areas of research may include studies (1) developing the data for use in an assessment that uses data-derived UFs, (2) evaluating when and how data-derived UFs can be used, or (3) pursuing other related areas of research.

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